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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,000	11/06/2000	Jon A. Wolff	Mirus.018.01	8513

7590 10/27/2003

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,000	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11-14,16-22,24-26,28-31,33-36,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *4 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 5, 10, 15, 23, 27, 32, 37 and 38 have been canceled. Claims 1-4, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36, 39 and 40 remain pending.

Election/Restriction

This application contains claims 4 and 40 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 8-11-03 have been fully considered but they are not persuasive. In future responses please use double spacing. The response should begin with support for the amendments followed by arguments regarding each rejection. In the response filed 8-11-03, applicants' representative did not address each indefiniteness rejection or the double patenting rejection. To be considered "responsive," each rejection must be addressed individually.

Claim Rejections - 35 USC ' 112

I. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The phrase "an injector" does not have support in the specification as originally filed. Support cannot be found on pg 2, lines 28-29, pg 3, lines 2, 3 and 14, pg 4, lines 32, pg 5, lines 5-7, pg 10, line 20, pg 16, lines 10-16, pg 17, lines 8-31, pg 23, lines 16-23, pg 25, line 32, through pg 26, line 1 or pg 31, lines 9-12, as stated in the response filed 8-11-03, on pg 6.

The phrase "distal to the occlusion" does not have support in the specification as originally filed. Support cannot be found on pg 16, lines 10-16, pg 23, lines 22-25, Example 3 on pg 25, Example 7 on pg 30, or Example 8 on pg 31, as stated in the response filed 8-11-03, on pg 6.

The term "superficialis" in claim 11 does not have support on pg 26 and is new matter.

The term "profundus" in claim 12 does not have support on pg 26 and is new matter.

II. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to

detectable levels in muscle cells of said limb, does not reasonably provide enablement for the methods claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 requires inserting an injector into a limb blood vessel of a mammal, applying a device external to mammalian skin for occluding blood vessels in the limb, and injecting a solution of the polynucleotides into the lumen of the vessel. Claims 6-9, 11-14, 16-22, 24-26, 28, 31 and 33-36 require delivery to specific muscles within the limbs. Claim 39 requires inserting an injector into a limb blood vessel of a mammal, applying pressure using a device external to mammalian skin, injecting a solution of the polynucleotides into the lumen of the vessel, and maintaining function of the limb.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art of record (Miller (1995, FASEB J., Vol. 9, pages 190-199; pg 198, column 1); Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, 1st ¶; pg 65, 1st ¶ under Conclusion section); Verma (Sept. 1997, Nature, Vol. 389, pages 239-242; entire article; pg 240, sentence bridging col. 2-3); Crystal (1995, Science, Vol. 270, page 404-410; pg 409).

The art at the time of filing taught that not all polynucleotides injected into a limb occluded by a tourniquet were expressed in skeletal muscle. Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, page 2197-2203) taught administering adenoviral particles encoding LacZ into a femoral artery and vein occluded using a tourniquet; expression occurred in hepatocytes but not in muscle cells of the limb (page 2201, col. 2, 2nd ¶).

The specification teaches administering naked plasmid DNA encoding a marker protein to an artery of the arm or leg and obtaining expression in muscle cells of the arm or leg, respectively. The specification does not teach delivering DNA to a leg blood vessel and expressing the DNA in arm skeletal muscle. The specification does not teach delivering DNA to an arm blood vessel and expressing the DNA in leg skeletal muscle.

It cannot be determined how targeting a cell as broadly claimed is affected by the location of the blood vessel injected, the type of polynucleotide (adenovirus vs. naked plasmid DNA), the method of occlusion (tourniquet vs. clamps, balloon catheter), or the method of immunosuppressing (administering vs. not administering an immunosuppressive agent). Specifically, the requirements for targeting muscle cells within the limb cannot be determined. Clarification is required.

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter.

The specification does not provide an enabled use for mere delivery of a polynucleotide to a cell. For the delivery to have an enabled use, it must encode a protein that is expressed to detectable levels in the cell. Therefore, the claims should recite a final step of obtaining detectable levels of expression of the protein.

Applicants have not provided any arguments regarding these matters of enablement.

III. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step a) remains unclear because it does not require the blood vessel is part of the mammal. While the claim requires inserting an injector into a limb blood vessel of a mammal, the claim does not state the injector is inserted into a mammal or that the injector is inserted into a limb blood vessel of a mammal in vivo.

Claim 1, step b) remains unclear because it does not require the blood flow to be impeded within the mammal or within the blood vessel receiving the polynucleotide. While the claim requires applying device external to mammalian skin, the claim does not require the "mammalian skin" belongs to the mammal to which an injector is inserted. The phrase "for occluding blood vessels in the limb" is an intended use and may not occur; therefore, it is unclear whether the blood vessel is occluded. In addition, the phrase does not clearly set for the limb being occluded is the limb to which the injector is inserted. Finally, the phrase "external to mammalian skin" does not clearly set forth that the device is applied to the skin; as written, it appears the device is applied anywhere outside of mammalian skin.

Claim 1 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell.

Claims 8, 9, 26 and 29 remain and claim 12 as newly amended is indefinite for reasons of record regarding the term "anterior."

Claims 13, 14, 21, 22 and 25 remain and claim 17 as newly amended is indefinite for reasons of record regarding the term "posterior."

Claims 9, 14, 22 and 24 remain indefinite for reasons of record regarding the term "superficial."

The phrase "wherein externally occluding blood vessels consists of compressing mammalian skin" (claim 33) remains unclear because the phrase "for externally occluding blood vessels" in parent claim 1 is an intended use and may not occur, and because the claim does not clearly set forth a step of "compressing mammalian skin."

The metes and bounds of what applicants consider "compressing" skin remain unclear (33-36). Is pinching the skin encompassed by the claim? If the polynucleotide is injected in the arm, does the claim encompass "compressing" the skin of the foot? There should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel by "compressing" skin. Similarly, there should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel using a tourniquet, cuff or sphygmomanometer.

Claims 34-36 remain indefinite because a tourniquet or cuff is not "applied over the skin." A tourniquet or cuff is placed on an arm, leg, etc. Pressure may be applied to

a blood vessel using a tourniquet or cuff. But a tourniquet or cuff is not "applied over the skin."

The metes and bounds of "cuff" remain unclear (claims 35, 36). The term does not have a defined meaning in the art. The specification defines "cuff" as a device for impeding blood flow in a blood vessel (page 5, line 13). While a sphygmomanometer cuff can be envisioned, and the specification states tourniquets are "cuff," other cuffs cannot be envisioned. Thus, the metes and bounds of devices encompassed by the term "cuff" cannot be determined. Does the cuff have to be applied to the outside of the mammal or is a string around the blood vessel a cuff? The definition provided in the specification is confusing. Is a cuff a "device for impeding blood flow through mammalian internal blood vessels" (line 13) or a "device applied to exterior to the mammal=s skin and touches the skin in a non-invasive manner" (line 14)? It cannot be determined which definition is to be applied. Therefore, the metes and bounds of the term cannot be determined.

Claim 39, step a) remains unclear because it does not require the blood vessel is part of the mammal. While the claim requires inserting an injector "into a limb blood vessel of the mammal", the claim does not state the injector is inserted into a mammal or that the blood vessel is still in the mammal.

Claim 39, step a) remains unclear because it does not require the blood flow to be impeded within the mammal or within the blood vessel receiving the polynucleotide. While the claim requires "applying pressure to a blood vessel... ...by a device external to mammalian skin", the claim does not require the "mammalian skin" belongs to the

mammal to which the injector is inserted, that the "device" is applied to the "blood vessel" or that the "device" is applied to the mammal to which the injector is inserted. Finally, the phrase "external to mammalian skin" does not clearly set forth that the device is applied to the skin; as written, it appears the device can apply pressure by being merely being outside of mammalian skin.

Claim 39 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell.

Claim 39 as newly amended is indefinite because it is unclear how "wherein function is not affected by the delivery process" further limits "maintaining function of the limb." If the limb maintains function, the limb is not affected by delivery.

Claim 39 as newly amended is indefinite because "the delivery process" lacks antecedent basis.

Applicants have not provided any arguments regarding these matters of indefiniteness.

Claim Rejections - 35 USC ' 102

The rejection of claims 1, 3, 6-9, 11-14, 16-22, 24-26, 28-31 and 39 under 35 U.S.C. 102(b) as being anticipated by Sferra (April 10, 1997, Human Gene Therapy, Vol. 8, pages 681-687) has been withdrawn because Sferra did not insert an injector into a limb blood vessel or apply a device external to mammalian skin.

The rejection of claims 1-3, 8-10, 13, 14 and 39 under 35 U.S.C. 102(e) as being anticipated by Wolff (US Patent 5,693,622 Dec. 2, 1997) has been withdrawn because Wolff did not insert an injector into a limb blood vessel or apply a device external to mammalian skin.

The rejection of claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31 and 39 under 35 U.S.C. 102(e) as being anticipated by Nabel (U.S. Patent, 5,910,488 filed 1-1-95) has been withdrawn because Nabel did not insert an injector into a limb blood vessel or apply a device external to mammalian skin.

The rejection of claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Nabel (U.S. Patent, 5,698,531, filed 1-23-95) has been withdrawn because Nabel did not insert an injector into a limb blood vessel or apply a device external to mammalian skin.

IV. Claims 1, 3, 33-35 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Milas taught administering adenoviral particles distally to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet applied to the skin of the rat. The claims require injecting the polynucleotides thereby delivering the polynucleotides to skeletal muscles. Milas meets the limitation of the claims because the polynucleotide is injected as claimed. The limitation of "for delivering polynucleotides to a skeletal muscle cell" in claims 1 and 39 is an intended use and does not bear patentable weight because it may not occur. However, the method of Milas inherently results in delivery of the adenovirus to skeletal muscle

because Fig. 3, pg 2200, shows delivery to the entire area of the leg including skeletal muscle.

Applicants argue Milas taught delivery exclusively to hepatocytes. Applicants' argument is not persuasive because the claim merely requires injection of the polynucleotides. The phrase "thereby delivering the polynucleotides" is not a separate step in the claim. In addition, the adenovirus was delivered throughout the leg as evidenced by Fig. 3 on pg 2200.

Double Patenting

The rejection of claims 1-3, 37 and 39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,265,387 has been withdrawn because claim 1 of '387 does not require inserting an injector into a limb blood vessel.

The rejection of claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/391260 has been withdrawn because the application is abandoned.

V. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 09/707117. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of delivering polynucleotides

into limb blood vessels occluded using a device external to mammalian skin for delivery to skeletal muscle cells.

VI. Claims 1-3, 37 and 39 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,379,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of '966 is an obvious species of claims 1-3, 37 and 39 in the instant application.

VII. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/917154. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of inserting an injector into blood vessels of the limb, applying a device to the external skin and injecting a polynucleotide into the blood vessel.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER